

Effect of Exogenous Thyroid Hormone Intake on the Interpretation of Serum TSH Test Results

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Introduction

The dosage of thyroid hormone for hypothyroid patients is usually set such that the TSH reading is within the reference range. At this dosage the physician regards the patient as being “balanced,” yet the patient often complains that this dosage is not sufficient to restore his or her feeling of well being.^[1,11] This method of determining the optimum dosage of thyroid hormone is based on the assumption that the TSH results can always be interpreted in the same way regardless of whether or not the patient is on thyroid hormone medication. This paper will use a control systems approach to hypothesise that this assumption is incorrect.

The hypothesis presented in this paper is supported by the data presented in the McKenna et al. study.^[12]

The Thyroid System

A block diagram of the thyroid system is presented in Figure 1. The thyroid gland produces T_3 and T_4 under the controlling influence of thyroid stimulating hormone (TSH) secreted by the pituitary gland. The T_3 and T_4 produced by the thyroid gland are released into the blood stream for distribution to all metabolically active cells. The levels of T_3 and T_4 in the blood stream are sensed by the thyrotrophs of the anterior pituitary gland and compared with the desired levels predetermined by hypothalamic thyrotrophin releasing hormone (TRH). In effect, the TRH provides a set point about which to regulate the serum T_3 and T_4 levels.^[4,5]

If the serum T_3 and T_4 levels fall, the pituitary gland secretes more TSH which stimulates the thyroid gland to produce more T_3 and T_4 . Conversely, if the

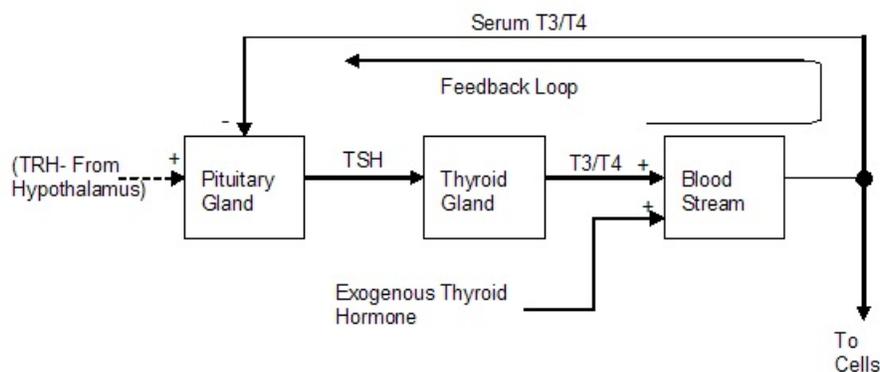


Figure 1. Block diagram of the thyroid system.

serum T_3 and T_4 levels rise, the pituitary gland secretes less TSH, so causing the thyroid gland to produce less T_3 and T_4 . Hence, there exists a negative feedback loop, the purpose of which is to regulate serum T_3 and T_4 at the desired level as the demand for T_3 and T_4 varies.

Exogenous thyroid hormone passes directly into

the blood stream, adding to thyroid hormone produced endogenously. The combined exogenous and endogenous hormone begin to raise the serum T_3 and T_4 levels. However, the negative feedback loop quickly acts to compensate for the increased thyroid hormone level by reducing TSH, hence reducing the output of T_3 and T_4 from the thyroid gland. As the exogenous

dose of T_3/T_4 increases, so the proportion of endogenously produced T_3/T_4 in the blood serum decreases.

Depending on the combined “gain” in the pituitary gland and/or the thyroid gland, the decrease in the endogenous production of T_3/T_4 may be less than, equal to, or greater than the increase in exogenous thyroid hormone intake. This variation in the ratio of endogenous to exogenous thyroid hormone results in under, exact or over-compensation respectively as described in this paper.

As the exogenous dosage increases, the feedback action results in a significant reduction in TSH. The reduced TSH is accompanied by a relatively insignificant change in the serum T_3 and T_4 levels up to the point where TSH suppression occurs. At that point, the T_3 and T_4 output of the thyroid gland can no longer

be significantly reduced.

In Figures 1 through 6, the conversion of T_4 into T_3 , which takes place in several tissues but mainly the liver, kidneys and thyroid gland,^[6] has been ignored in order to simplify the model.

TSH Levels

A patient who is not on thyroid hormone replacement therapy, and whose thyroid gland is producing too much T_3/T_4 , is said to be hyperthyroid. As this condition develops, negative feedback action compensates by reducing TSH. At the point where TSH suppression first occurs, the serum T_3/T_4 levels are almost unchanged, as shown in Figure 2.

As the condition progresses further, the serum

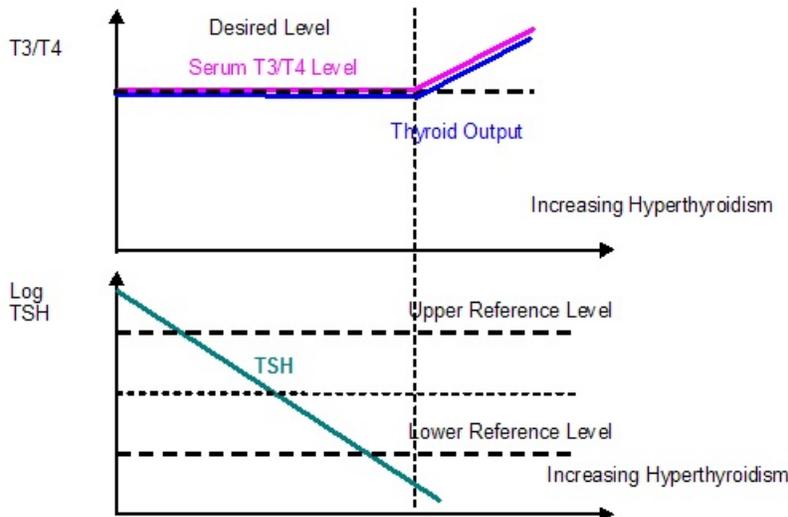


Figure 2. Serum T_3/T_4 and TSH levels in progressing hyperthyroidism.

T_3 and T_4 levels rise. By the time the patient has developed symptoms of hyperthyroidism and presented them to his or her physician, it is not unreasonable to assume that a diagnosis based on the suppressed TSH level can confidently be made (provided that the pituitary gland is working normally). It is considered by some authorities that if severe enough and left untreated, this situation will lead to cardiac problems and reduced bone mineral density.

However, when a hypothyroid patient is started on a low dose of thyroid hormones, the feedback loop begins to compensate for the exogenous supply of T_3/T_4 . The feedback loop compensates by reducing TSH and hence endogenous T_3/T_4 production,

as shown in Figure 3. As the exogenous dose increases further, TSH decreases, but the serum T_3/T_4 levels do not start to increase until TSH suppression occurs. A suppressed TSH does not necessarily mean, therefore, that the patient has become hyperthyroid with the attendant risks mentioned above.

The physician, of course, will want to avoid over-treating the patient. To avoid over-treatment, the physician is unlikely to prescribe a dose of thyroid hormone higher than that which has suppressed the patient’s TSH. The physician, then, uses the suppressed TSH level as his or her primary gauge of the adequacy of treatment. However, the hypothesis presented in this paper proposes that a suppressed TSH in a patient undergoing thyroid hor-

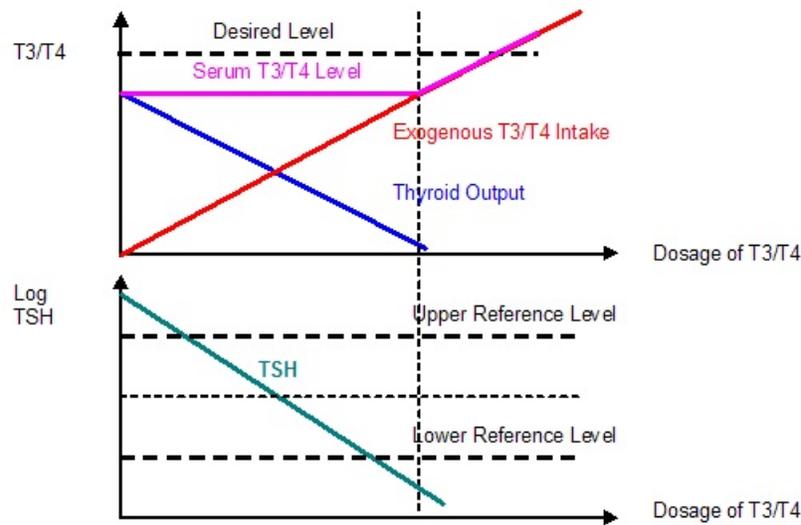


Figure 3. Serum T3/T4 and TSH levels with increasing exogenous dose.

Thyroid hormone treatment should not be the primary determinant of the adequacy of treatment. The hypothesis further proposes that the patient's pituitary/thyroid feedback loop has effectively lowered endogenous thyroid hormone production and suppressed the TSH as the appropriate physiological adjustment to the patient's exogenous thyroid hormone.

However, the suppressed TSH does not accurately gauge whether the patient's exogenous thyroid hormone dosage is insufficient, excessive, or adequate. This determination can be made only through consideration of the tissue effects of exogenous thyroid hormone.

If the proposed hypothesis is correct, then the

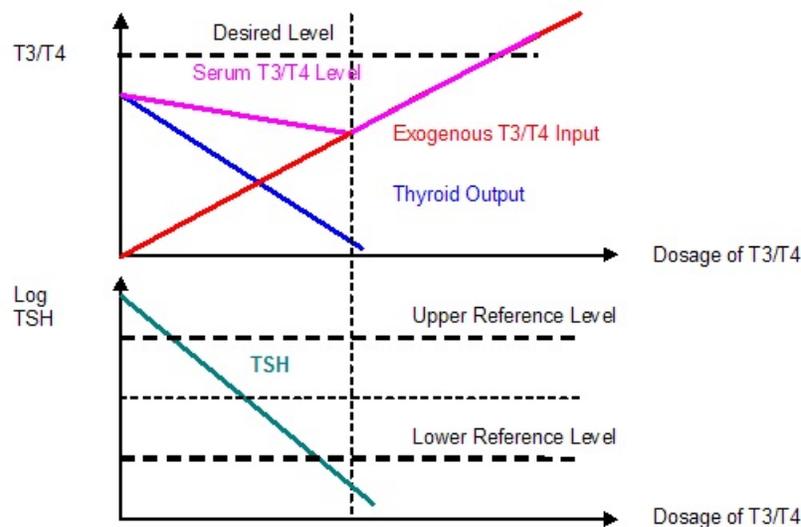


Figure 4. Serum T3/T4 and TSH levels with increasing exogenous dose (feedback loop over-compensating).

patient's TSH level has ceased to be a useful test of the adequacy of thyroid hormone intake. Instead, the proper action for the physician is to look to test results that indicate tissue effects of thyroid hormone to decide whether the patient's thyroid hormone intake is too low, too high, or adequate. Such tests include the basal temperature and/or

pulse rate, serum T_3/T_4 level, and symptoms.

Exact Compensation. Figure 3 illustrates exact compensation whereby the increase in exogenous T_3/T_4 intake is exactly matched by a decrease in thyroid gland output up to the point where TSH suppression occurs. Because of the action of the feedback loop, therefore, a suppressed TSH when

the patient is on medication cannot necessarily be interpreted as meaning that the patient is hyperthyroid—not unless the exogenous dosage really is excessively high. Indeed, it is quite likely that the serum T_3/T_4 levels have not increased at all.

Over Compensation. Figure 4 illustrates over-compensation whereby the reduction in endogenous T_3/T_4 production exceeds the increase in the exogenous dose. It can be seen that the serum T_3/T_4 levels reduce up to the point where TSH suppression occurs. It is also evident that the serum T_3/T_4 levels show no increase over their pre-treatment levels until the exogenous dose exceeds that required to just cause TSH suppression.

Again, a suppressed TSH does not necessarily mean that the patient is hyperthyroid. Furthermore, an exogenous dose that does not exceed that which just causes TSH suppression may actually result in

an unintended reduction in serum T_3/T_4 levels, as manifested by an unexpected increase in the severity of the patient's symptoms.

Under Compensation. Under-compensation, whereby the reduction in endogenous T_3/T_4 production is exceeded by the increase in exogenous T_3/T_4 dose, is illustrated in Figure 5. It can be seen that although there is some increase in the serum T_3 and T_4 levels relative to the pre-treatment levels, up to TSH suppression, the full benefit of treatment is not gained until the exogenous dosage exceeds that required for TSH suppression.

Again, a suppressed TSH does not necessarily mean that the patient is hyperthyroid. Furthermore, whilst there may be a modest reduction in the severity of the patient's symptoms up to TSH suppression, this reduction may well be less than the physician hoped for.

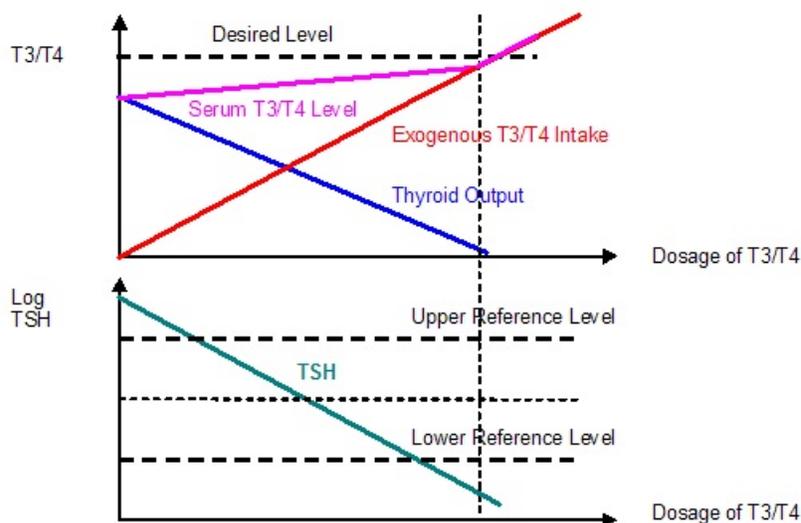


Figure 5. Serum T_3/T_4 and TSH levels with increasing exogenous dose (feedback loop under-compensating).

Relationship Between TSH and T_4 . In the preceding analysis it has been assumed, for clarity, that there is an inverse logarithmic relationship between T_4 and TSH. However, Professor Rudolf Hoermann et al. have shown that a much more dynamic and non-linear relationship exists between T_4 and TSH.^[2]

Some authorities have spoken of “the exquisite sensitivity of TSH.” The new model proposed by Professor Rudolf Hoermann et al.,^[2] however, shows that “the response of pituitary TSH depends on the deviation of circulating free T_4 from an optimum set point and may turn out less vigorous and exaggerated as the magnitude of the deviation decreases.” Figure 3 must therefore be modified as

shown in Figure 6 (a piecewise linear presentation of the T_4 /TSH relationship has been used for clarity).

It can be seen from Figure 6 that there is effectively a “dead-band” in the region of the set point where the feedback action will be weaker. In electronic control systems, a dead-band may be deliberately introduced to prevent instability. It is suggested that the dead-band in the thyroid feedback loop may have a similar function. Nevertheless, the pituitary-thyroid-pituitary feedback loop will still compensate for the exogenous dose by reducing the output of the thyroid, whatever the actual form of the T_4 /TSH relationship. However, physicians who set the dosage of thyroid hormone

at a level which reduces TSH to about mid range will be working, albeit unwittingly, at the portion of the TSH/T₄ relationship where the pituitary

TSH response is weakest. This will compound the errors and uncertainties involved when using TSH levels to set the thyroid hormone dose.

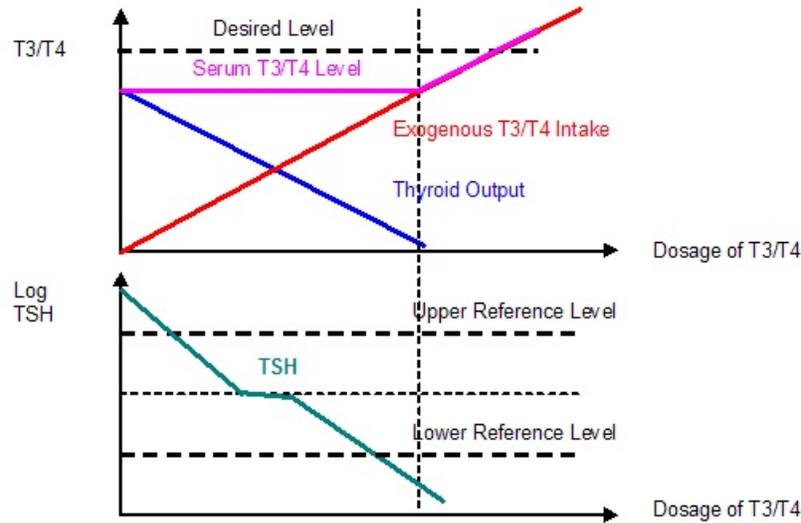


Figure 6. Serum T3/T4 and TSH levels with increasing exogenous dose (non-linear T4/TSH relationship).

Discussion

In diabetes, the correct dose of insulin required can be determined by regularly checking the blood glucose levels. The blood glucose measurement is a direct check on the downstream effect of insulin and no inferential measurements are involved.

In hypothyroidism, on the other hand, the only measurements that are equivalent to the glucose in the insulin example, as downstream effects of thyroid hormone on the metabolic processes in the cells, are basal temperature^[7] and metabolic rate measurements.^[3,8,9,10] However, it is more usual for physicians treating hypothyroidism to infer that the thyroid hormone level in cells is normal from an upstream measurement—serum T₃/T₄ levels. This is not a reliable inference to make because numerous mechanisms of thyroid hormone resistance can substantially alter the relationship between the serum and cell T₃/T₄ levels, as Tjorve et al.^[3] have described.

When the serum T₃/T₄ levels are then inferred from a measurement of TSH instead of being measured directly, two levels of inference have taken place, the results of which should be treated with a high index of suspicion.

Conclusions

1. The TSH reading alone is valid only when the patient is not on thyroid hormone replacement

therapy, but even then there are two levels of inference between it and the thyroid hormone levels in cells other than the pituitary thyrotrophs. Within the double inference there will be many interpretation errors.

2. The sensitivity of the TSH reading varies relative to the set point, and is least sensitive in the region of the set point.
3. Hypothyroid patients whose thyroid hormone replacement dose is being regulated against the TSH reading alone are being maintained in an under-treated state and are correct to assert that they feel better on a higher dose. Therefore, hypothyroid patients should not have their thyroid hormone dosages set by reference to their TSH readings.
4. Clinical studies should be carried out to confirm the hypothesis presented in this paper.

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